Syllabus

Topics in Clinical Trials
Spring Semester 2016
Rice University course STAT 630
University of Texas GSBS course GS01 1813

Time: **9:25 – 10:40 a.m., Tuesday and Thursday**
Locations: **The locations of the lectures will change, but all locations are at M.D. Anderson.**

Instructors:

Peter F. Thall, PhD rex@mdanderson.org, 713-794-4162, Office FCT4.6014
Brian P. Hobbs , PhD bp@mdanderson.org, 713-794-4633 Office FCT 4.6050

Prerequisites:
STAT 410: INTRODUCTION TO REGRESSION AND STATISTICAL COMPUTING
STAT 431: OVERVIEW OF MATHEMATICAL STATISTICS

Lecture Schedule

Thall	Hobbs
Tues 1/19 – FCT5.5049	Tues 3/08: - FCT2.4144 (Room A)
Thurs 1/21 – R2.2628 Main Building	Thurs 3/10: – ACB4.1281ab
Tues 1/26 – R2.2628 Main Building	Tues 3/15: - FCT2.4144 (Room A)
Thurs 1/28 – R2.2628 Main Building	Thurs 3/17: – FC1.2050
Tues 2/2 – Y7.5302 Main Building	Tues 3/22: - FCT2.4144 (Room A)
Thurs 2/4 – FC1.2050	Thurs 3/24: - FCT2.4144 (Room A)
Tues 2/9 – FCT2.4144 (Room A)	Tues 3/29: – FCT3, Room 5
Thurs 2/11 - Y7.5302 Main Building	Thurs 3/31: - FC1.2050
Tues 2/16 – FCT3, Room 1	Tues 4/5: – B6.4804
Thurs 2/18 – FC1.2050	Thurs 4/7: - FC1.2050
Tues 2/23 - R2.2628 Main Building	Tues 4/12: - FCT2.4144 (Room A)
Thurs 2/25 - R2.2628 Main Building	Thurs 4/14: - R2.2628 Main Building
	Tues 4/19: - FCT2.4144 (Room A)
Feb 29 – March 4 SPRING BREAK	
Wednesday May 4 : TAKEHOME FINAL DUE	

Software Download site https://biostatistics.mdanderson.org/SoftwareDownload

Homeworks and Exam

Your course grade will be based on homework assignment and a takehome final exam. Homeworks will be a combination of problems to be solved, clinical trial designs to be constructed including computer simulations, and write-ups of published papers . In your homework write-ups:

1) **Begin by stating the problem or giving reference(s) of the paper(s) to be explained.**
2) **Clearly define any notation before using it.**
3) **Use clear, complete, grammatically correct sentences.**
4) **Be complete, but as brief as possible.**
5) **You may use any references you like, but all of your work must be your own.**

Reference Books

1. Cook TD, Demets DL (Ed.) Introduction to Statistical Methods for Clinical Trials. Chapman & Hall/CRC, 2008.
2. Friedman, Furberg, and DeMets: Fundamentals of Clinical Trials. 4th ed.: New York: Springer, 2010
3. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons, 2004.
4. Kosorok MR, Moodie EEM (eds). Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine. SIAM, 2016.
5. Yuan Y, Nguyen HQ, Thall PF. Bayesian Designs for Phase I-II Clinical Trials. Taylor & Francis. In press.

The lecture topics listed below will be covered as time permits. It is very unlikely that all topics listed below will be covered. Additionally, the topics may not be covered in the order given.

Lecture Topics for Dr. Thall

1. Why Conduct a Clinical Trial?
    a. Medicine and Statistics
    b. Randomness, Probability, and Bayesian Statistics
    c. Sequential Decision Making in Clinical Trials
    d. "Phase I → Phase II → Phase III" : A Dysfunctional Paradigm
2. Comparing Treatments
    a. Estimation and Comparison
    b. Simpson's Paradox
    c. Bias and Bias Correction
    d. Randomization and Causality
    e. Adaptive Randomization
    f. Group Sequential Designs
3. Monitoring discrete single outcomes in phase II clinical trials
    a) Beta-binomial models and methods for binary outcomes [1]
    b) Dirichlet-multinomial design paradigm for multiple outcomes [2,3]
4. Exponential -gamma models and methods for event times in phase II [2]
5. Patient heterogeneity in phase II clinical trials
    a) Bayesian methods based on analysis of variance models [5]
    b) Methods based on Bayesian hierarchical models [6]
6. Phase I-II dose-finding based on Efficacy-Toxicity trade-offs
    a) The homogeneous case: Trinary and bivariate binary outcomes [7]
    b) Personalized dose-finding to incorporate covariates [8]
7. Dose-finding with two agents [9]
8. Dealing with multiple toxicities in phase I using total toxicity burden [10]
9. Utility-based dose-finding
    a) Single agent designs [11-13]
    b) Two agent designs [14-15]
    c) A two-cycle design [16]
10. Optimizing dose and schedule [17-20]
11. Phase II/III designs [21-23]
12. Prior effective sample size in Bayesian clinical trial design [30-32]
13. Dynamic treatment regimes and multi-stage therapies [24-28, 35,36]
14. Data Mining*: Post Hoc* Evaluation of Dynamic Treatment Regimes [33,34]

15. Bayesian sensitivity analysis for treatment comparisons based on nonrandomized data [29]

References for Professor Thall's Lectures

1. Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* 50: 337-349, 1994.
2. Thall PF, Simon R, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat in *Medicine* 14:357-379, 1995.
3. Thall PF, Sung H-G. Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Stat in Medicine*, 17:1563-1580, 1998
4. Thall PF, Wooten LH, Tannir N. Monitoring event times in early phase clinical trials: some practical issues. *Clinical Trials.* 2:467-478, 2005.
5. Wathen JK, Thall PF, Cook, JD, Estey EH. Accounting for patient heterogeneity in phase II clinical trials. *Stat in Medicine*. 27:2802-2815, 2008.
6. Thall PF, Wathen JK, Bekele BN, Champlin RE, Baker LO, Benjamin RS. Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. *Stat in Medicine*, 22: 763-780, 2003.
7. Thall PF, Cook JD. Dose-finding based on efficacy-toxicity trade-offs. Biometrics, 60:684-693, 2004.
8. Thall PF, Nguyen H, Estey EH. Patient-specific dose-finding based on bivariate outcomes and covariates. *Biometrics.* 64:1126-1136, 2008.
9. Thall PF, Millikan RE, Mueller P, Lee S-J. Dose-finding with two agents in phase I oncology trials. *Biometrics*, 59:487-496, 2003.
10. Bekele BN, Thall PF. Dose-finding based on multiple toxicities in a soft tissue sarcoma trial*. J American Statistical Association,* 99:26-35, 2004.
11. Thall PF, Nguyen HQ. Adaptive randomization to improve utility-based dose-finding with bivariate ordinal outcomes. J Biopharmaceutical Statistics 22:785-801, 2012.
12. Thall PF, Szabo A, Nguyen HQ, Amlie-Lefond CM, Zaidat OO. Optimizing the concentration and bolus of a drug delivered by continuous infusion*. Biometrics*. 67:1638-1646, 2011
13. Thall PF, Nguyen HQ, Zohar S, Maton P. Optimizing sedative dose in preterm infants undergoing treatment for respiratory distress syndrome. J American Statistical Assoc. 109:931-943, 2014.
14. Houede N, Thall PF, Nguyen H, Paoletti X, Kramar A. Utility-based optimization of combination therapy using ordinal toxicity and efficacy in phase I/II trials*. Biometrics*. 66:532-540, 2010.
15. Thall PF, Nguyen HQ, Zinner RG. Parametric dose standardization for two-agent combinations in phase I-II trials with ordinal outcomes. Revised for *JRSS-C.*
16. Lee J, Thall PF, Ji Y, Muller P. Bayesian dose-finding in two treatment cycles based on the joint utility of efficacy and toxicity. J American Statistical Assoc. 110:711-722, 2015.
17. Braun TM, Yuan Z, Thall PF. Determining a maximum tolerated schedule of a cytotoxic agent. *Biometrics,* 61:335-343, 2005.
18. Braun TM, Thall PF, Nguyen H, de Lima M. Simultaneously optimizing dose and schedule of a new cytotoxic agent. *Clinical Trials*, 4:113-124, 2007.
19. Thall PF, Nguyen HQ, Braun TM, Qazilbash M. Using joint utilities of the times to response and toxicity to adaptively optimize schedule-dose regimes. Biometrics. 69:673-682, 2013.
20. de Lima M, Giralt S, Thall PF**,** Silva LP, Wang X, Jones RB, Komanduri K, Braun TM**,** Nguyen HQ**,** Champlin R, Garcia-Manero G. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for relapsed AML or MDS: a dose and schedule finding study*. Cancer.* 116:5420-5431, 2010.
21. Thall PF, Simon R, Ellenberg SS. Two-stage selection and testing designs for comparative clinical trials. Biometrika 75: 303-310, 1988.
22. Schaid DJ, Wieand HS, Therneau TM. Optimal two-stage screening designs for survival comparisons. *Biometrika* 77: 507-513. 1990.
23. Thall PF, Nguyen HQ, Wang X, Wolff JE. A hybrid geometric phase II/III clinical trial design based on treatment failure time and toxicity. *J Statistical Planning and Inference*. 142:944-955, 2012.
24. Thall PF, Millikan R, Sung, H-G. Evaluating multiple treatment courses in clinical trials. *Stat in Medicine*, 19: 1011-1028, 2000

25. Thall PF, Logothetis C, Pagliaro L, Wen S, Brown MA, Williams D, Millikan R. Adaptive therapy for androgen independent prostate cancer: A randomized selection trial including four regimens. *J National Cancer Institute*. 99:1613-1622, 2007
26. Wang L, Rotnitzky A, Lin X, Millikan R, Thall PF. Evaluation of viable dynamic treatment regimes in a sequentially randomized trial of advanced prostate cancer. *J. American Statistical Association*. In press.
27. Thall PF, Wooten LH, Logothetis CJ, Millikan R, Tannir NM. Bayesian and frequentist two-stage treatment strategies based on sequential failure times subject to interval censoring. *Stat in Medicine*. 26:4687-4702, 2007.
28. Thall PF, Sung H-G, Estey EH. Selecting therapeutic strategies based on efficacy and death in multi-course clinical trials. *J American Statistical Association*, 97:29-39, 2002.
29. Thall PF, Champlin RE, Andersson BE. Comparison of 100-day mortality rates associated with IV busulfan and cyclophosphamide versus other preparative regimens in allogeneic bone marrow transplant for chronic myelogenous leukemia: Bayesian sensitivity analyses of confounded treatment and center effects. *Bone Marrow Transplantation*, 33: 1191-1199, 2004.
30. Morita S, Thall PF, Mueller P. Determining the effective sample size of a parametric prior. Biometrics. 64:595-602, 2008.
31. Morita S, Thall PF, Mueller P. Evaluating the impact of prior assumptions in Bayesian biostatistics. Statistics in Biosciences. 2:1-17, 2010.
32. Morita S, Thall PF, Mueller P. Prior effective sample size in conditionally independent hierarchical models. Bayesian Analysis. 7:591-614, 2012
33. Wahed AS, Thall PF. Evaluating joint effects of induction-salvage treatment regimes on overall survival in acute leukemia. J Royal Statistical Society, Series C (Applied Statistics). 62:67-83, 2013.
34. Xu Y, Mueller P, Wahed A, Thall PF. Bayesian nonparametric estimation for dynamic treatment regimes with sequential transition times. J American Statistical Assoc. (with discussion). In press.
35. Hernan, M.A., Brumback, B. and Robins, J.M. Marginal structural models to estimate the causal effect of Zidovudine on the survival of HIV-positive men. Epidemiology. 11:561-570, 2000.
36. Moodie, E.E.M, Richardson, T.S. and Stephens, D.A. Demystifying optimal dynamic treatment regimes. Biometrics. 63:447-455, 2007.

Lecture Topics for Dr. Hobbs

1. Introduction to clinical trials, basic principles
2. Commonly used study designs
3. Randomization and blinding
4. Outcome adaptive randomization
5. Sample size and power calculation
6. Group sequential designs
7. Interim data monitoring, data safety and monitoring board
8. Meta-analysis and study reporting
9. Phase II – single arm designs, one-stage and multi-stage designs, designs based on predictive probability and Bayes factors
10. Phase II – randomized designs, Bayesian adaptive randomization designs
11. Commensurate priors and historical data in randomized comparative trials